

REMARKS/ARGUMENTS

Claims 1-62 are pending in the captioned application. Claims 57-62 have been withdrawn as drawn to a non-elected invention, while claims 1-56 stand rejected. Applicants respectfully request reconsideration and allowance of the claims in view of the amendments and the following arguments.

Claims 1-31 stand rejected again as containing new matter. Specifically, the Examiner regards the phrase “with a phosphatase activatable label” as new matter. Applicants respectfully disagree. Nonetheless, in an effort to expedite prosecution, Applicants hereby cancel the phrase rendering the rejection moot.

The claims are also rejected as containing new matter due to the recitation in claims 1-31 of “without first separating by charge of said detectable species from the reaction mixture”, and the recitation in claims 32-56 of “without first separating by charge of said labeled polyphosphate from the reaction mixture”. The Examiner states that the specification does not appear to recite the limitations anywhere. Applicants respectfully disagree.

In response, Applicants submit that a skilled person provided with the specification would clearly understand that in the claimed methods, the labeled polyphosphate or detectable species does not need to be separated by charge prior to detection. For example, the specification at page 4, lines 6-9, states, “The labeled polyphosphate then reacts with phosphatase or a phosphate or polyphosphate transferring enzyme to produce free label with a signal readily distinguishable from

the phosphate bound dye”. Applicants submit that the phrase “readily distinguishable” clearly indicates that no separation by charge is required. Later in the same paragraph (page 4, lines 12-14), the specification states that, “After sufficient time is allowed for the polymerization reaction, which may range from milliseconds to several minutes, and detecting the presence or absence of signal, solid support may be separated from solution...”. Again, Applicants submit that the description clearly indicates that no separation by charge is required here prior to signal detection. Further, in describing the terminal-phosphate-labeled nucleotide, the label is clearly defined on page 12, lines 1-6, which again indicates that separation by charge is not required of the current claimed methods.

Similarly, the specification provides support for the amendment to claims 32-56 as well. For example, the specification states that “in embodiments including terminal-phosphate-labeled nucleotides having four or more phosphates in the polyphosphate chain, it is within the contemplation of the present invention that the labeled polyphosphate by-product of phosphoryl transfer may be detected without the use of phosphatase treatment. Upon incorporation of the nucleoside monophosphate, the label polyphosphate by-product may be detected due to its enhanced fluorescence.” (Page 13, lines 25-33). Applicants submit that the specification taken as a whole, clearly describes sequencing methods which do not require separation by charge, prior to the detecting step, of either the detectable species or the labeled polyphosphate from the reaction mixture. The new matter rejection of the claims can not be sustained and should be withdrawn.

Claims 1-7, 9, 11-18, 20-23, 27-38, 40, 42-45, 47, 49-50, 55 and 56 stand rejected under 35 U.S.C. §102 (b) as being anticipated by Williams et al (WO/2001/94609). Applicants respectfully disagree.

Applicants previously argued that the amended claims require the detection step to be performed without separation by charge of polyphosphate or detectable species, thus is not anticipated by Williams et al. The Examiner states in response that Williams et al. does teach a method on page 24, lines 15-26 which does not require the separation based on charge. Applicants submit that the Examiner is mischaracterizing the reference.

Applicants first submit that the Williams et al. reference is related to charge-switch nucleotides, see e.g., Title, Abstract and Brief Summary of the Invention (page 3). The charge-switch nucleotides carry a molecular charge different from the charge carried by the phosphate fluorophore cleaved off the nucleotide (page 3, lines 13-29), thus they migrate to different electrodes (page 3, line 30 to page 4, line 2). Applicants submit that the methods of Williams et al. clearly require a physical separation of the charge-switch nucleotides from the phosphate fluorophore cleaved off the nucleotides. This is further evidenced by Williams et al.'s discussion of their methods (page 20, line 22 to page 21, line 3).

Nothing in the section of Williams et al. cited by the Examiner (page 24, lines 15-26) suggests the method could be performed without a step of separation by charge. Applicants submit that the cited method clearly uses "a charge-switch NTP", having a fluorophore attached to the gamma-phosphate. This implies that the method

includes a step of separation by charge. This is because the fluorophore label, whether part of the nucleotide or released from the nucleotide, has the same fluorescent property therefore can not be differentiated without being physically separation. Applicants submit that unlike the Examiner's assertion, the teachings of Williams et al. on page 24 do imply separation by charge, although it was not explicitly stated. Williams et al. clearly states that "a charge-switch NTP" was used, and therefore a separation step based on charge has to be part of the method.

Applicants submit that the rejection of claims 1 and 32 over Williams et al. should be withdrawn. Therefore the 35 U.S.C. §102 (b) rejection of claims 1-7, 9, 11-18, 20-23, 27-38, 40, 42-45, 47, 49-50, 55 and 56 should also be withdrawn.

Claims 8 and 39 are again rejected under 35 U.S.C. §103(a) as being unpatentable over Williams in view of Wittwer et al (USPN 6,174,670). Claims 10 and 41 are again rejected under 35 U.S.C. §103(a) as being unpatentable over Williams in view of Keller et al (USPN 5,656,462). Claims 19 and 46 are again rejected under 35 U.S.C. §103(a) as being unpatentable over Williams in view of Lichenwalter et al (USPN 5,683,875). Claims 23-25 are again rejected under 35 U.S.C. §103(a) as being unpatentable over Williams in view of Hattori et al (USPN 5,821,095). Claims 25 and 26 are again rejected under 35 U.S.C. §103(a) as being unpatentable over Williams in view of Bronstein et al (USPN 5,112,960). These rejections are respectfully traversed. As stated above, Williams et al. does not disclose or even suggest independent claims 1 or 32, upon which these claims depend. In view

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of this, Applicants submit that the 35 U.S.C. §103(a) rejections should also be withdrawn.

Applicants respectfully assert that the claims are in allowable form and earnestly solicit the allowance of claims 1-56.

Early and favorable consideration is respectfully requested.

Respectfully submitted,

GE Healthcare Bio-Sciences Corp.

By: 
Yonggang Ji
Reg. No.: 53,073
Agent for Applicants

GE Healthcare Bio-Sciences Corp.
800 Centennial Avenue
P. O. Box 1327
Piscataway, New Jersey 08855-1327

Tel: (732) 980-2875
Fax: (732) 457-8463

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Name: _____

Melissa Leck